Epidemiology and Pathology of Oral Squamous Cell Carcinoma in a Multi-ethnic Population: Analysis of 154 cases over 12 years in Qatar

Orwa Elaiwy (orwa87@gmail.com)
Hamad Medical Corp https://orcid.org/0000-0002-9037-5118
Walid El Ansari
Hamad Medical Corporation
Moustafa Al-Khalil
Hamad Medical Corporation
Adham Ammar
Hamad Medical Corporation

Research article

Keywords: Oral cancer, Squamous Cell Carcinoma, Multi-ethnic, Surgical Resection Margin Evaluation, head and neck cancer

Posted Date: August 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41593/v1

Abstract

Background: Oral cancer (OC) is a neoplastic process of the oral cavity that has high mortality and significant effects on patients' aesthetics. Majority of OC is oral squamous cell carcinoma (OSCC) and resection remains the most frequent therapy. Recurrence is the main cause of tumor-related mortality.

Material and methods: A retrospective review of patients' charts in Hamad Medical Corporation studied of 154 adults who were diagnosed as OSCC in between 2006- 2018 . The data extracted was demographic, pathologic and clinical. All patients with oral cavity tumors other than squamous cell carcinoma were excluded.

Results: Males comprised the majority of the sample, mean age was 46.93 years. Tongue was the most common location. Majority of the patients were diagnosed at early stages and a small subset of patients had histologically-proven local recurrence.

Conclusion: Demographics of OSCC patients in Qatar revealed an unprecedented male predominance with a significant younger portion. Most patients were non-nationals, mainly from South Asia. No significant association was found between age groups and local recurrence against multiple parameters. Improving of follow-up system is suggested.

Conclusion: The young male predominance of OSCC patients in Qatar is unprecedented worldwide. Most patients were non-Qataris, mainly from South Asia. Loss of follow-up was a challenge in assessing the long term outcomes of OSCC. Our findings suggest the need for a more vigilant surveillance approach to oral lesions particularly in male South-Asian patients, as well as improving the follow-up strategies.

Background

Oral cancer (OC) is a neoplastic process of the oral cavity (from the lips to the fauceses' anterior pillars) [1], and males are more affected [2]. It is a global public health issue as it is the eighth most common cancer (> 300,000 cases annually) [3], characterized by its high mortality and multiple effects on aesthetics of patients [1]. The incidence and mortality rates of OC vary globally and are higher in developing nations, particularly India and other South/eastern Asia regions, France, Slovenia, Slovakia and Hungary [4; 5; 2]. Such incidence and mortality differences between high and low income countries, and the increased OC related mortality in societies with low-development and high societal disparities suggest that society-related factors e.g., culture and lifestyle influence its tumorigenesis [2; 6].

About 90–95% OC is oral squamous cell carcinoma (OSCC) [7], classified into 3 Grades, from well-differentiated (Grade I) to poorly-differentiated (Grade III) [8]. Curative resection and reconstruction remain the most frequent therapy to maintain the form and function of the head and neck area [1]. Despite recent breakthroughs in treatment modalities, OSCC still has poor prognosis, due to local aggressiveness and metastasis, where recurrence arises in ≈ 30% of cases [9]. Local and regional recurrences are the main

cause of OSCC-related mortality, where the 5-year survival drops from 92% in recurrence-free patients to 30% in patients with recurrence [10; 9].

The literature reveals several gaps. First, in terms of breadth, some studies assessed the clinical and pathological features of OSCC [6, 11, 12, 13], others focused only on surgical aspects [e.g., 10, 14, 15]; with few studies simultaneously considering the clinical, epidemiological, histopathological and surgical parameters in order to gauge prognosis [e.g., 11, 8, 16]. Likewise, there remains debate about histology-based vs clinical-based risk-assessment scoring systems in predicting prognosis [17, 8, 16; 5]. Second, some studies assessed only tongue OSCC [5, 18, 19], despite that floor of mouth is a common OSCC site [8, 16]. Third, in terms of stage, research focused on early stages of OSCC [e.g. 18, 19], despite evidence linking advanced OSCC stages to poorer prognosis [12]. Fourth, with a few exceptions [20, 13, 15], many studies had modest sample sizes (17–126 patients) [12, 8, 21, 10, 19, 22, 23, 24]. Fifth, most studies did not have representative samples of the countries they were conducted in, comprising single center studies [12, 8, 13, 15], with rare exceptions of single country multi-center studies [20, 19, 23]. Sixth, with few exceptions [12, 5], most investigations were among ethnically homogenous populations [6, 13], despite evidence linking certain racial groups to poorer prognosis [25, 26, 27]. Seventh, there is paucity of OSCC literature from the Middle East and North Africa (MENA) and sub-Saharan Africa. Many MENA countries lack national cancer reporting systems [7], and OSCC management and outcomes data were absent in many sub-Saharan studies [28]. Likewise, few studies assessed the relationship between age and OSCC prognosis, despite the reported inconsistency in the relationship between age and OSCC prognosis [29, 12, 30, 31, 16]. In addition, no literature investigated the association between age and perineural invasion and lymphovascular invasion as independent prognostic factors, despite their importance in prognosis and management [3]. Finally, research assessed the associations between recurrence, and tumor size, stage, and margins [e.g., 12, 23], but no literature examined the possible association between local recurrence and age.

There is no published data about OSCC for the State of Qatar, despite its ethnically diverse population [32]. Therefore, this retrospective study at the sole reference center in Qatar reviewed all OSCC cases of all stages [August 2006-December 2018] involving any location of the oral cavity, employing a generous sample size (154 ethnically diverse patients) and examined a wide range of demographic, clinical, epidemiological, histopathological and surgical parameters. The specific objectives assessed:

- A range of demographic, clinical, epidemiological, histopathological and surgical characteristics of OSCC;
- Associations between local recurrence and tumor site, age, and stage [T-stage] and nodal metastasis (N-stage); and,
- Associations between age and pathologic stage (T-stage), nodal metastasis (N-stage), histological grade, lymphovascular invasion and perineural invasion.

Material And Methods

Ethics, settings and study design

This study was approved by the medical research centre/Institutional research board (IRB) at Hamad Medical Corporation (HMC) (protocol number MRC-01-20-136). This a retrospective review of patients' charts at Hamad General Hospital, Doha (The largest tertiary care center in Qatar) and Rumailah Hospital, Doha (A multi-specialty center that includes Qatar's reference ENT, cranial and maxillofacial departments), both part of (HMC, equivalent of Ministry of Health).

Study population

The population studied consists of 154 adults who were histologically diagnosed as OSCC in between August 2006- December 2018. Our sample is representative of all cases of OSCC in Qatar because any cancer case must be referred to the national cancer MDT which meets on a weekly basis at Hamad General Hospital.

Data collection

By searching the hospitals' and MDT's database, we reviewed charts of all patients diagnosed and operated for OSCC (August 2006- December 2018). The data included were demographic (gender, age, nationality), pathologic (tumor anatomical site, histological variant of SCC, grade, depth of invasion, pTNM stage, lymphovascular invasion, perineural invasion, margin status and tumor bed status), as well as clinical (follow-up period and histologically –proven recurrence). The follow-up was calculated starting from the initial surgery till the patient's last visit to HMC, with any period lasting between 6 months and 1 year counted as 0.5. Local recurrence was defined as histologically proven re-emerging of OSCC within 3 years after initial surgery [19]. Any OSCC after more than 3 years was considered a metachronous primary tumor [second primary].

Inclusion and exclusion criteria

All patients who had histologically-proven squamous cell carcinoma of the oral cavity that were registered in the Head and Neck cancer "MDT" between August 2006- December 2018 were included in the study. All patients with oral cavity tumors other than squamous cell carcinoma were excluded, as well as patients with squamous cell carcinoma in anatomical sites of the head and neck other than oral cavity.

Statistical analysis

Data was analyzed using the Statistical Package SPSS v20 transferred. Categorical variables were summarized using frequencies and percentage; continuous variables were summarized using means and standard deviation. Chi-square test assessed the relationships between categorical variables. Significance level was set at $p < 0.05$. The distribution of some variables e.g. DOI was skewed to the left, so the median is used.

Results

Table 1 shows selected demographic characteristic of the sample. Males were a majority, mean age was 46.93 years, with nearly equally-distributed age brackets. South Asian nationalities comprised about two-thirds of the sample. Patients from the India comprised more than one third of the sample (39.6%), followed by Pakistanis (9.7%) then Qatari nationals and Bangladeshi (7.8% each) (data not presented)

Table 1
Selected Demographic Characteristic of the sample (N = 154)

Characteristic	Number of cases*	Value = N (%)
Gender (N %)	154	
Males		141 (91.6)
Females		13 (8.6)
Male to female ratio		10.9:1
Age bracket at Diagnosis (years)	154	
< 40		48 (31.2)
41–50		54 (35.1)
> 50		52 (33.8)
Age at Diagnosis (years, M [a] ± SD [b])	154	46.93 ± 12.304
Nationality group	154	
Middle East and North Africa [c]		36 (23.4)
South Asian [d]		104 (67.5)
Rest of the world [e]		14 (9.1)

***** Number of cases with data available for analysis; [a] Mean; [b] Standard Deviation; [c] including Iran, [d] including Philippines, [e] including Sudan;

Table 2 depicts selected specimen and tumor characteristic of the sample. The majority of patients had resections, while less had biopsies only. The most common location of primary tumor was the tongue (50% of cases), followed by the buccal mucosa, and mean depth of invasion (DOI) was 8.8 mm (Median DOI = 7 mm) A majority of OSCC was of the conventional variant, and grade 2 was the most common histological grade, comprising about half of the cases. Where data was available, most cases exhibited no lymphovascular invasion, but perineural invasion was found in more than one third of the patients. Most of the sample had surgical negative margins; however, about half the patients had close margins (i.e. negative but < 5 mm). For all patients where a tumor bed specimen was submitted, only one case had a positive tumor bed margin. Mean follow up period was 2.38 years. Of the patients who underwent

surgery, only a minority had histologically-proven recurrence, however 40.7% of patients were lost to follow-up (and therefore recurrence status is unknown).

Table 2
Selected Specimen and Tumor Characteristic of the sample (N = 154)

Characteristic	Number of cases*	Value = N (%)
Specimen		
Specimen type	152	
Biopsy		52 (34.2)
Resection		100 (65.8)
Tumor		
Location of primary tumor (detailed)	154	
Border of tongue		77 (50)
Floor of mouth/ventral tongue		7 (4.5)
Buccal mucosa/buccal sulcus		47 (30.5)
Soft palate/tonsil area		5 (3.2)
Alveolar mucosa/ gingiva/ retro molar area		4 (2.6)
Lower lip		7 (4.5)
Buccogingival		3 (1.9)
Maxillary sinus and hard palate		1 (0.6)
Tongue base, floor of mouth and epiglottis		3 (1.9)
Location of the primary tumor (groups)	154	
Buccal mucosa and palate		59 [38.3)
Tongue		82 [53.2)
Lip		7 [4.5)
Floor of mouth and maxilla		6 [3.9)
Depth of invasion (M [a] ± SD [b], mm)		8.799 ± 6.2
Depth of invasion (MED [c] ± SD [b], mm)		7 ± 6.2
Pathological staging (pTN) [d]	102	

***** Number of cases with data available for analysis; [a] Mean; [b] Standard Deviation; [c] Median; [d] For resection specimens only; [e] Only for cases for which data was available; [f] Oral Squamous Cell Carcinoma; [g] Patients who were followed for < 3 years or died < 3 years after surgery with cause of death unavailable

Characteristic	Number of cases*	Value = N (%)
Histological grading	154	
Grade 1		45 (29.2)
Grade 2		77 (50)
Grade 3		32 (20.8)
Lymphovascular invasion [e]	100	
Yes		13 (13)
No		87 (87)
Perineural invasion [e]	109	
Yes		42 (38.5)
No		67 (61.5)
Dysplasia	153	
Yes		21 (13.7)
No		132 (86.3)
Surgical margins [d]	104	
Positive		11 (10.6)
Negative		39 (37.5)
Close		54 (51.9)
Tumor bed margin [d]	97	
Not submitted		15 (15.5)
Submitted positive		1 (1)
Submitted negative		81 (83.5)
Histological variants of OSCC [f]	154	
Conventional		150 (97.4)
Verrucous		1 (0.6)

***** Number of cases with data available for analysis; [a] Mean; [b] Standard Deviation; [c] Median; [d] For resection specimens only; [e] Only for cases for which data was available; [f] Oral Squamous Cell Carcinoma; [g] Patients who were followed for < 3 years or died < 3 years after surgery with cause of death unavailable

Characteristic	Number of cases*	Value = N (%)
Basaloid		1 (0.6)
Keratoacanthoma-like variant		1 (0.6)
Hybrid (verrucous with conventional)		1 (0.6)
Follow up (M [a] ± SD [b], years)	100	2.38 ± 1.86
Recurrence [d]	103	
Yes		12 (11.7)
No		49 (47.6)
Unknown [g]		42 (40.8)

***** Number of cases with data available for analysis; [a] Mean; [b] Standard Deviation; [c] Median; [d] For resection specimens only; [e] Only for cases for which data was available; [f] Oral Squamous Cell Carcinoma; [g] Patients who were followed for < 3 years or died < 3 years after surgery with cause of death unavailable

Table 3 shows the pathological staging of the sample. The majority of patients had early stage disease, and about half the sample had no lymph node metastasis. Due to the large number of combined stage values, the pathological staging was further categorized into T-stage (primary tumor) and N-stage (nodal metastasis). Patients with early T-stage disease (T1 and T2) comprised more than half the sample (39.8% and 26.2% respectively). About half of the patients had no nodal metastasis.

Table 3

Pathological staging (pTN) of the sample [a] (N = 154)

Characteristic	Number of cases*	Value = N (%)
pTN	102	
T1N0		24 (23.5)
T1N1		3 (2.9)
T1N2		0 (0)
T1N2B		3 (2.9)
T1NX		8 (7.8)
T2N0		13 (12.7)
T2N1		9 (8.8)
T3N0		7 (6.9)
T3N1		6 (5.9)
T3N2		1 (1)
T3N2A		1 (1)
T3N2B		1 (1)
T3N3B		1 (1)
T3NX		1 (1)
T4N0		6 (5.9)
T4N1		0 (0)
T4N2		0 (0)
T4N2B		2 (2)
T4N2C		1 (1)
T4N3B		2 (2)
T4NX		0 (0)
TXN0		2 (2)
TXNX		3 (2.9)
T-stage	103	

[a] For resection specimens only; ***** Number of cases with data available for analysis;

Characteristic	Number of cases*	Value = N (%)
T1		41 (39.8)
T2		27 (26.2)
T3		18 (17.5)
T4		11 (10.7)
TX		6 (5.8)
N-stage	103	
N0		52 (50.5)
N1		18 (17.5)
N2		1 (1)
N2A		1 (1)
N2B		12 (11.7)
N2C		1 (1)
N3		0 (0)
N3B		3 (2.9)
NX		15 (14.6)
[a] For resection specimens only; * Number of cases with data available for analysis;		

Discussion

This study assessed the epidemiological demographic, clinical, epidemiological, histopathological and surgical characteristics of OSCC in Qatar. In terms of gender, the majority of our patients were males, with a M:F ratio of ≈ 10.9:1. Hence our findings support that OSCC has a male predominance globally [13]. The global OSCC M:F ratio is about 5.5:2.5 [33], ranging from 1.2:1 [5] to 3.02:1 [16]. Such range is similar to most Arab nations [7]. Our OSCC M:F ratio was the highest worldwide, probably due to the unique demographics in Qatar. The large numbers of single young male workers and expats working in Qatar have resulted in a country having has the highest M:F ratio worldwide (3.15:1) [32].

As for age, globally, most OSCC patients are > 45 years of age at first diagnosis, [median 62 years], with only 6% of patients < 45 years [12]. In contrast, about one third of our patients were < 41 years, a proportion that is significantly higher than other studies globally [13, 6, 9] and regionally [20]. Our sample's mean age was 46.9 years (range 18–78), suggesting that OSCC patients in Qatar are slightly younger than their counterparts in the region [7]. Again, this is probably because the majority of the population in Qatar are young and middle-aged individuals [32]. Age groups correlation was studied

against multiple parameters [T-stage, N-stage, grade, lymphovascular and perineural invasion] and no statistically significant correlation was identified.

In terms of nationality, most patients were not Qatari nationals. Indians comprised largest proportion of OSCC our patients (39.6%), reflecting the country's demographics, as Indians are the largest ethnic group of the expat population living in Qatar [34]. Individuals from South Asian countries were also well represented, in agreement with the higher OSCC incidence in South Asia [5].

The most common site of primary tumor in the current study was the tongue (53.2%), in contrast with other studies where buccal mucosa was the most common location, especially in South Asians [e.g., 16]. Nevertheless, our finding is in concordance with most of published literature, where the tongue was the most common [15, 7, 35, 13, 12].

The current study observed a mean DOI of 8.8 mm (median 7 mm, range 1.5–25 mm), slightly deeper than the 5.7 mm mean DOI reported in United Kingdom [12] and 6.3 mm in Finland [36], although it was less than the 12.9 mm reported in one international multicenter study [37]. DOI in OSCC is an important variable in predicting nodal metastasis and hence it impacts on the management and prognosis [38].

Pathological staging is a prognostic factor, where the T-stage (primary tumor) is an important factor in selecting the management option and predicting nodal metastasis, recurrence and survival [12]. A majority of our sample (66%) was early stage (T1 and T2), probably attributed to an efficient cancer referral system in Qatar that is vigilant for suspected cancer patients, and hence the early referral and detection. However, the N-stage is also another key prognostic factor, where generally, about half the OSCC patients have nodal metastasis at diagnosis [39]. Across our sample, 50.5% of patients who underwent resection had no nodal metastasis, while 17.5% were N1 stage. A proportion of patients who underwent resection [14.6%] did not undergo neck dissection at surgery, and subsequently were classified as NX. Our practice is in line with others, where the decision to sample cervical lymph nodes is usually based upon the primary tumor [T-stage], with the T1 patients spared from neck dissection if radiologically not suspicious [3]. Therefore, our finding of NX patients is probably due to the early stage nature of the disease among the majority of our sample.

The World Health Organization's classification grades OSCC as well differentiated (Grade 1), moderately differentiated (Grade 2) and poorly differentiated (Grade 3), based upon the pathologist's evaluation of keratinization, pleomorphism, and mitosis [12]. Globally, whilst many OSCC are low histological grade, grade 2 moderately differentiated tumors form the majority of cases [13, 15]. The current study is in agreement, since the majority of patients (50%) were grade 2 followed by grade 1 (29.2%) [Figure 1].Some researchers employ grade as a part of the risk-assessment to predict prognosis and survival [17].

In terms of the histological variants of OSCC, some authors have linked particular variants with better prognosis and other variants with less favorable outcomes [40]. Generally, the conventional variant comprises a majority of the cases, with other variants involving up to 15% of cases [41]. We are in

support, the conventional variant in the present study comprised a majority (97.4%), with each of the other six variants each having a single case (0.6% each) (Fig. 2).

The margin status in the main resection specimen has special significance since its involvement is a negative prognostic factor, implying increased recurrence and poorer survival [18]. Of the resection cases in the current study, 10.6% had positive margin in the main resection specimen, 37.5% had negative margin (> 5 mm clearance), and more than half had close margin [negative but < 5 mm clearance]. Our proportion of cases with close margins was higher than other studies [e.g., 12, 5], probably due to the high dependence of surgeons at our institution on the tumor bed margin frozen section [performed in 84.5% of eligible cases] that provides surgeons with high certainty of the completeness of the excision. Such certainty is evidenced by that across our sample, tumor bed was submitted for frozen section in 84.5% of eligible cases, and of those which were submitted, only one case was positive while all remaining cases were negative. Notwithstanding, the importance of intraoperative margin sampling and examination by frozen section [tumor bed margin sampling] to outcomes remains controversial, with some authors suggesting that this practice has no effect on survival and outcome [15].

A body of research defines follow-up for recurrence and survival at 3 and 5 year milestones [e.g., 12] with a minority implementing a 2 and 5 year time points [9]. In our 100 resection cases where follow-up data was available, mean follow-up period was 2.38 years, slightly less than the 3 years criteria, probably attributed to the fact that most of our OSCC patients were not Qataris, with many returning to their home countries after initial treatment in Qatar

Local recurrence is a key prognostic factor in OSCC patients where some authors reported a median survival drop from 6.4 years in recurrence-free patients to 3.5 years in those with recurrence [9]. Recurrence influences both the 5-year and the disease-free survival in OSCC patients [8]. Of the resection cases in our study, 11.7% had histologically-proven recurrence, 47.6% were recurrence-free after ≥ 3 years of follow-up, and 40.8% had unknown recurrence (lost follow-up before reaching the 3-year milestone).

Statistical analysis yielded no significant association between local recurrence and each of tumor site, age group, T- and N-stage. This can be attributed to the limited number of cases with local recurrence and the significant portion of patients who lost follow-up.

The study has limitations. Better data quality about survival would have been beneficial. Smoking history and recreational habits (e.g., tobacco chewing) were not regularly documented, which would have been useful in investigating possible risk factors. A major challenge was the loss of follow-up, due to the mobile expat nature of the population in Qatar, with high losses to follow-up due to relocation. Nevertheless, the study has important strengths. There is no published data about OSCC for the State of Qatar, despite its ethnically diverse population. We employing a generous sample (154 patients) and examined a wide range of demographic, clinical, epidemiological, histopathological and surgical parameters. Our sample is representative of all cases in the country as our center is the sole reference center in Qatar that reviews all OSCC cases of all stages involving any location of the oral cavity.

Conclusion

The young male predominance of OSCC patients in Qatar is unprecedented worldwide. Most patients were non-Qataris, mainly from South Asia. Although most patients had negative margins upon resection, a majority of these margins were close. A small subset of patients had histologically-proven local recurrence, but loss of follow-up was a challenge in assessing the long term outcomes of OSCC. No significant association was found between age groups and local recurrence against multiple parameters. Our findings suggest the need for a more vigilant surveillance approach to oral lesions particularly in male South-Asian patients, as well as improving the follow-up strategies.

Declarations

Acknowledgements:

The publication of this article was funded by Qatar National Library.

Availability of data and materials:

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions:

Conceived and designed the study: AA and MA. Collected data: OE. Analyzed the data: OE and WE. Wrote the paper: OE and WE. All authors read and approved the final manuscript.

Competing interests:

The authors declare that they have no competing interests.

Consent for publication:

Not applicable.

Ethics approval and consent to participate:

Ethical approval was given by the medical research centre/Institutional research board (IRB) at Hamad Medical Corporation (HMC), Doha, Qatar.

References

1. Omura K. Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol. 2014;19(3):423–30.

2. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol. 2015;8(9):11884.
3. D'Cruz AK, Vaish R, Dhar H. Oral cancers: current status. Oral Oncol. 2018;87:64–9.
4. Gupta N, Gupta R, Acharya AK, Patthi B, Goud V, Reddy S, Garg A, Singla A. Changing Trends in oral cancer-a global scenario. Nepal journal of epidemiology. 2016;6(4):613.
5. Rodrigues PC, Miguel MC, Bagordakis E, Fonseca FP, De Aquino SN, Santos-Silva AR, Lopes MA, Graner E, Salo T, Kowalski LP, Coletta RD. Clinicopathological prognostic factors of oral tongue squamous cell carcinoma: a retrospective study of 202 cases. Int J Oral Maxillofac Surg. 2014;43(7):795–801.
6. Iamaroon A, Pattanaporn K, Pongsiriwet S, Wanachantararak S, Prapayasatok S, Jittidecharaks S, Chitapanarux I, Lorvidhaya V. Analysis of 587 cases of oral squamous cell carcinoma in northern Thailand with a focus on young people. Int J Oral Maxillofac Surg. 2004;33(1):84–8.
7. Al-Jaber A, Al-Nasser L, El-Metwally A. Epidemiology of oral cancer in Arab countries. Saudi Med J. 2016;37(3):249.
8. Lindenblatt RD, Martinez GL, Silva LE, Faria PS, Camisasca DR, Lourenço SD. Oral squamous cell carcinoma grading systems–analysis of the best survival predictor. Journal of oral pathology medicine. 2012;41(1):34–9.
9. Wang B, Zhang S, Yue K, Wang XD. The recurrence and survival of oral squamous cell carcinoma: a report of 275 cases. Chinese journal of cancer. 2013;32(11):614.
10. Liu CH, Chen HJ, Wang PC, Chen HS, Chang YL. Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone. Kaohsiung J Med Sci. 2013;29(10):554–9.
11. Arduino PG, Carrozzo M, Chiecchio A, Broccoletti R, Tirone F, Borra E, Bertolusso G, Gandolfo S. Clinical and histopathologic independent prognostic factors in oral squamous cell carcinoma: a retrospective study of 334 cases. Journal of oral maxillofacial surgery. 2008;66(8):1570–9.
12. Jerjes W, Upile T, Petrie A, Riskalla A, Hamdoon Z, Vourvachis M, Karavidas K, Jay A, Sandison A, Thomas GJ, Kalavrezos N. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. Head Neck Oncol. 2010;2(1):9.
13. Pires FR, Ramos AB, Oliveira JB, Tavares AS, Luz PS, Santos TC. Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. Journal of Applied Oral Science. 2013;21(5):460–7.
14. Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. Oral Oncol. 2015;51(5):464–9.
15. Buchakjian MR, Tasche KK, Robinson RA, Pagedar NA, Sperry SM. Association of main specimen and tumor bed margin status with local recurrence and survival in oral cancer surgery. JAMA Otolaryngology–Head Neck Surgery. 2016;142(12):1191–8.
16. Dissanayaka WL, Pitiyage G, Kumarasiri PV, Liyanage RL, Dias KD, Tilakaratne WM. Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. Oral surgery, oral medicine, oral pathology and oral radiology. 2012;113(4):518–25.

17. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML, Wang BY. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol. 2005;29(2):167–78.
18. Maxwell JH, Thompson LD, Brandwein-Gensler MS, Weiss BG, Canis M, Purgina B, Prabhu AV, Lai C, Shuai Y, Carroll WR, Morlandt A. Early oral tongue squamous cell carcinoma: sampling of margins from tumor bed and worse local control. JAMA Otolaryngology–Head Neck Surgery. 2015;141(12):1104–10.
19. Chang AM, Kim SW, Duvvuri U, Johnson JT, Myers EN, Ferris RL, Gooding WE, Seethala RR, Chiosea SI. Early squamous cell carcinoma of the oral tongue: comparing margins obtained from the glossectomy specimen to margins from the tumor bed. Oral Oncol. 2013;49(11):1077–82.
20. Al-Rawi NH, Talabani NG. Squamous cell carcinoma of the oral cavity: a case series analysis of clinical presentation and histological grading of 1,425 cases from Iraq. Clinical oral investigations. 2008;12(1):15–8.
21. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. Br J Oral Maxillofac Surg. 2013;51(7):594–9.
22. Varvares MA, Poti S, Kenyon B, Christopher K, Walker RJ. Surgical margins and primary site resection in achieving local control in oral cancer resections. Laryngoscope. 2015;125(10):2298–307.
23. Dillon JK, Brown CB, McDonald TM, Ludwig DC, Clark PJ, Leroux BG, Futran ND. How does the close surgical margin impact recurrence and survival when treating oral squamous cell carcinoma? J Oral Maxillofac Surg. 2015;73(6):1182–8.
24. Jinnouchi S, Kaneko K, Tanaka F, Tanaka K, Takahashi H. Surgical outcomes in cases of postoperative recurrence of primary oral cancer that required reconstruction. Acta Medica Nagasakiensia. 2016;60(3):119–24.
25. Moles DR, Fedele S, Speight PM, Porter SR. The unclear role of ethnicity in health inequalities: the scenario of oral cancer incidence and survival in the British South Asian population. Oral Oncol. 2007;43(8):831–4.
26. Daraei P, Moore CE. Racial disparity among the head and neck cancer population. J Cancer Educ. 2015;30(3):546–51.
27. Osazuwa-Peters N, Massa ST, Christopher KM, Walker RJ, Varvares MA. Race and sex disparities in long-term survival of oral and oropharyngeal cancer in the United States. J Cancer Res Clin Oncol. 2016;142(2):521–8.
28. Faggons CE, Mabedi C, Shores CG, Gopal S. Head and neck squamous cell carcinoma in sub-Saharan Africa. Malawi Medical Journal. 2015;27(3):79–87.
29. Garavello W, Spreafico R, Gaini RM. Oral tongue cancer in young patients: a matched analysis. Oral Oncol. 2007;43(9):894–7.

30. Montoro JR, Hicz HA, de Souza L, Livingstone D, Melo DH, Tiveron RC, Mamede RC. Prognostic factors in squamous cell carcinoma of the oral cavity. Brazilian journal of otorhinolaryngology. 2008;74(6):861–6.
31. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, Sutton D, Errington D, Vaughan D. Survival following primary surgery for oral cancer. Oral Oncol. 2009;45(3):201–11.
32. Alrouh H, Ismail A, Cheema S. Demographic and health indicators in Gulf Cooperation Council nations with an emphasis on Qatar. Journal of Local Global Health Perspectives. 2013;2013(1):3.
33. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ, editors. WHO classification of head and neck tumours. International Agency for Research on Cancer; 2017.
34. De Bel-Air F. Demography, migration, and labour market in Qatar. 2014.
35. Maleki D, Ghojazadeh M, Mahmoudi SS, Mahmoudi SM, Pournaghi-Azar F, Torab A, Piri R, Azami-Aghdash S, Naghavi-Behzad M. Epidemiology of oral cancer in Iran: a systematic review. Asian Pac J Cancer Prev. 2015;16(13):5427–32.
36. Almangush A, Leivo I, Siponen M, Sundquist E, Mroueh R, Mäkitie AA, Soini Y, Haglund C, Nieminen P, Salo T. Evaluation of the budding and depth of invasion (BD) model in oral tongue cancer biopsies. Virchows Archiv. 2018 Feb 1;472(2):231-6.
37. Ebrahimi A, Gil Z, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, Kowalski LP, Kreppel M, Cernea CR, Brandao J. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA Otolaryngology–Head Neck Surgery. 2014;140(12):1138–48.
38. Brockhoff HC, Kim RY, Braun TM, Skouteris C, Helman JI, Ward BB. Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma. Head Neck. 2017;39(5):974–9.
39. Wreesmann VB, Katabi N, Palmer FL, Montero PH, Migliacci JC, Gönen M, Carlson D, Ganly I, Shah JP, Ghossein R, Patel SG. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. Head Neck. 2016;38(S1):E1192-9.
40. El-Mofty SK. Histopathologic risk factors in oral and oropharyngeal squamous cell carcinoma variants: an update with special reference to HPV-related carcinomas. Medicina oral, patologia oral y cirugia bucal. 2014;19(4):e377.
41. Pathak J, Swain N, Patel S, Poonja LS. Histopathological variants of oral squamous cell carcinoma-institutional case reports. Journal of oral maxillofacial pathology: JOMFP. 2014;18(1):143.

Figures

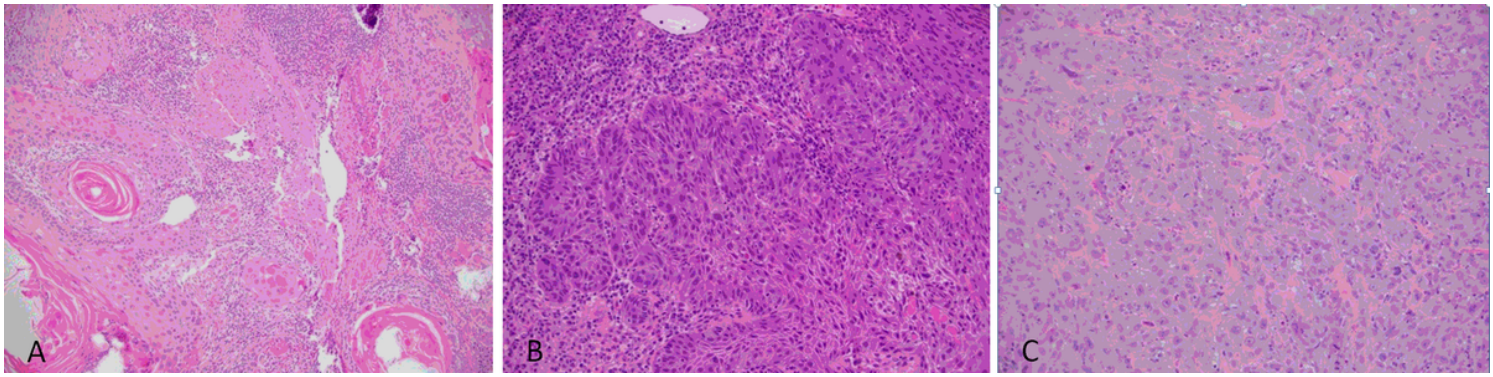

Figure 1

SCC grades. A: HE stained section ×200 magnification showing grade 1 SCC, B: HE stained section ×200 magnification showing grade 2 SCC and C: HE stained section ×200 magnification showing grade 3 SCC.

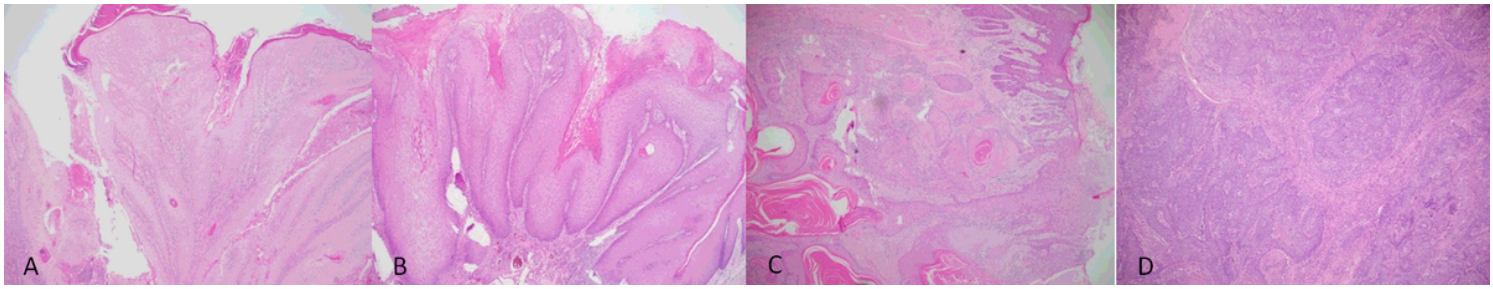

Figure 2

SCC variants. A: HE stained section ×40 magnification showing keratoacanthoma-like variant, B: HE stained section ×40 magnification showing verrucous variant, C: HE stained section ×40 magnification showing conventional variant and D: HE stained section ×40 magnification showing basaloid variant.